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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/430,735	10/29/1999	NNOCHIRI N. EKWURIBE	4012-113-DIV	7685

7590 10/01/2004

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EXAMINER	
CELSA, BENNETT M	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/430,735	EKWURIBE ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-49, 70-71 and 73-76, 78-81 and 83-100* is/are pending in the application.

4a) Of the above claim(s) *84,86-93 and 95-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-49,70,71,73-76,78-81,83,85 and 98-100* is/are rejected.

7)☒ Claim(s) *94* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/8/04 has been entered.

Information Disclosure Statement

The Information Disclosure statement (IDS PTO-1444 form) dated 8/26/04 is acknowledged. Please find attached an initialed PTO-1449 indicating Examiner consideration of the reference enumerated thereon.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 46-49, 70-71 and 73-76, 78-81 and 83-100 are currently pending.

Claims 46-49, 70-71, 73-76, 78-81, 83, 85, 94 and 98-100 are under consideration.

Claims 84, 86-93 and 95-97 are withdrawn from consideration as being directed to a nonelected invention.

Election/Restriction

2. Applicant's election without traverse of Group II (claims 46-52) in Paper No. 6 is acknowledged

Applicant's election without traverse of Met-Enk (Lys)(PEG_4)$(CH2)_{13}CH_3$ (E.g. Lys modified Met-Enk with hydrophilic PEG and hydrophobic alkyl) which reads on claims 46-49, 70-71, 73-76, 78-81, 83 , 85 , 94 and 98-100 is acknowledged. To the extent that the elected species was deemed nonobvious (in light of applicants arguments: see "Allowable Subject Matter" below) the search was expanded to include an additional reference containing a species within the scope of the generic claim (irrespective of the fact that the elected alkyl-PEG subgenus is still rejected) in which the reference was applied below for purposes of compact prosecution.

3. Claims 84, 86-93 and 95-97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Allowable Subject Matter

Claim 94 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The following is an examiner's statement of reasons for allowance: Applicant's arguments regarding nonobvious (e.g. unexptected results) relating to the rat data directed to this specific elected compound (e.g. page 47 of the application) was persuasive. However, this argument was not persuasive regarding the broader claims since it is not commensurate; and is insufficient to rebut anticipation/obvious of the elected subgeneric (e.g. alkyl-PEG-enkephalin peptide conjugate).

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably

accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Withdrawn Objection (s) and/or Rejection (s)

4. Applicant's arguments directed to the provisional double patenting rejections over Ekwuribe et al. 09/429,798 application were considered and deemed persuasive.

Outstanding Objection(s) and/or Rejection (s)

Claim Rejections - 35 USC 103

5. Claims 46-49, 70-71, 73-76, 78-81, 83, 85 and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yagi et al. US Pat. No. 5,061,691 (10/91) and Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) and further in view of the specification (e.g. abstract; page 2 and Examples, especially on pages 44-48) as evidence of inherency.

The present claims are directed to:

A method of inducing analgesia in a subject in need thereof by administering a drug conjugate *which crosses the blood-brain barrier* in which the conjugate comprising:

a. an "opioid" (e.g. met enkephalin or leu enkephalin) conjugated to an

b. "oligomer", wherein the oligomer comprises "one or more lipophilic moieties" coupled to "one or more "hydrophilic moieties".

Preferred "opioids" are the pentapeptides met/leu enkephalins YGGFM and YGGFL, respectively (YGGFM elected);

Preferred "lipophilic moieties are fatty acids, cholesterol, and C1-C26 alkyl (alkyls elected);

Preferred "hydrophilic moieties" are sugars and PEG (PEG elected). See claims 46-49.

Additionally, the claims recite that the administered conjugate:

i. effects "CNS mediated" analgesia (E.g. see claims 46, 83 and claims 98-100);

ii. "traverses the blood brain barrier in an amount that is greater than a corresponding control" (new claim 98);

iii. "wherein a corresponding unconjugated control does not cross the blood-brain barrier in analgesically effective amounts" (new claim 99);

iv. "wherein the conjugate crosses the BBB in a controlled manner which permits accumulation of sufficient quantities of the therapeutic in the brain to induce analgesia" (new claim 100).

Yagi et al teach that

a. opiate (e.g. enkephalin) receptors are present in the brain (e.g. CNS) and are responsible for the analgesic effects of administered opioids (e.g. "CNS mediated analgesia" : see Yagi col. 1, especially lines 5-17);

b. unmodified (e.g. unconjugated) enkephalins produce a "weak and short-lived analgesia following i.c.v./i.v. administration to mice and rats (e.g "unconjugated control does not cross the blood-brain barrier in analgesically effective amounts") and accordingly, the Yagi reference addresses efforts made (e.g. making of analogs of Met- and Leu-enkephalins) in order to promote *in vivo* delivery by overcoming art-recognized administration obstacles (e.g. enzymatic degradation; *ability to pass thru blood-brain* barrier; administration in oral dosage form etc.). See abstract; col. 1; and patent claims.

The Yagi et al. reference teaching differs from the presently claimed invention which achieves analgesic therapy (e.g enteral/parenteral administration) of opioids (e.g. especially peptide opioids Met- and Leu-enkephalins) by conjugating the opioids

(especially enkephalins) with a polymer which comprises lipophilic and hydrophilic moieties.

However, Ekwuribe teaches the stabilization of therapeutic agents (E.g. protease resistance and enhanced penetration) for in vivo administration (e.g. oral or parenteral) by conjugating with a polymer which comprises lipophilic and hydrophilic moieties. E.g. see abstract; col 1-4 (e.g. stabilization). Opioids, especially peptidic opioids such as endorphins and enkephalins are preferred therapeutic agents. See Abstract; col. 8 (lines 40-50); patent claims (especially claims 37-44). Therapeutic administration includes administration to humans via enteral (e.g. oral), parenteral, as well as other modes of physiological administration (E.g. see col. 12, especially lines 5-10; col. 13, especially lines 45-55; col. 24-col. 24) including opthalmic, topical, bronchial, rectal, iv, subcutaneous, intrathecal etc (e.g. see col. 25-26). See also patent claims 35-44.

One of ordinary skill in the art would have been motivated to conjugate opioids (e.g. especially peptide opioids Met- and Leu-enkephalins and analogs thereof) as disclosed in Yagi et al. in the manner of Ekuwuribe to achieve an analgesic composition overcoming the *in vivo* obstacles recited in the Yagi reference.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicants invention to achieve opioid (e.g. enkephalin) analgesic therapy by modifying the opioid with polymers comprising lipophilic and hydrophobic moieties as taught by Ekwuribe in order to obtain Astable therapeutic agents for in vivo parenteral/enteral delivery.

To the extent the presently claimed invention (e.g. claims 48-49, 83, 85) selects PEG (as hydrophilic moiety; preferably PEG2) and C1-C26 (as lipophilic moiety) the same is rendered obvious by Ekwuribe.

Ekwuribe teaches the preferential selection of PEG (especially PEG2-4) as the hydrophilic moiety and alkyls (e.g. CH3 and CH2mCH3 m is 1-125) as the lipophilic moiety in which the Drug is attached through a carbamate linkage adjacent to the PEG region of the polymer with the point of attachment of the carbamate bond between the polymers preferably is the amine function . See col. 13-14, especially col. 13 (lines 5-20); col. 14 (conjugates 2 and 3); col 14 (lines 30-60); patent claims (especially claims 34 and conjugates 2 and 3 described therein and claims 35-42 drawn to therapeutic methods employing enkephalin conjugates). Ekuwuribe further teaches the ability to vary the position and number of hydrophilic/lipophilic moieties to achieve optimization. E.g. see col. 14, lines 50-60.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicants invention to utilize an oligomer (or polymer) comprising PEG (e.g. PEG2) as a hydrophilic moiety and a C1-26 alkyl in light of the Ekwuribe teaching of the preferred selection of PEG2-4 as a hydrophilic moiety and alkyls (e.g. m is 1-125 with methyl disclosed) with optimization of hydrophilic/lipophilic groups suggested by Ekwuribe in which such optimization is well within the skill of the art.

Additionally, the Yagi et al. reference differs (if at all) from the presently claimed invention (as amended) by failing to disclose or suggest that administration of an *amphiphilic drug-oligomer conjugate* within the scope of the presently claimed invention which achieves

delivery (of the conjugate) across the blood brain barrier (BBB) of the subject (e.g. claims 46 and 83) " ... in a controlled manner which permits accumulation of sufficient quantities of the therapeutic in the brain to induce analgesia" (e. g. new claim 100).

However, the presently claimed analgesic conjugates rendered obvious by the above-recited references, must inherently produce the same *in vivo* effect (blood brain barrier delivery in a controlled manner and in sufficient quantities) because the same conjugate is applied (e.g. administered) in the same way in the same amount to the same subject. *In re Best*, 195 USPQ 430,433 (CCPA 1977). The specification provides evidence that the amphiphilic oligomer conjugates rendered obvious by the above references, are capable of (e.g. see present specification on page 2 and abstract) and indeed do traverse the blood brain barrier upon administration to subjects in the manner taught by the prior art references. See ***Ex parte Novitski***, 26 USPQ2d 1389 (B.P.A.I, 1993) (applicants own specification provides evidence of inherent effect produced upon drug administration); MPEP 2131.01(d) permits the citation of references or any other source of extrinsic evidence in order to show that a characteristic not disclosed in the reference is inherent.

6. Claims 46-49, 70-71, 73-76, 78-81, 83, 85, and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yagi et al. US Pat. No. 5,061,691 (10/91), Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) and the specification as applied to claims 46-49, 70-71, 73-76, 78-81, 83, 85 and 98-100 above, and further in view of Mensi-Fattohi et al. US Pat. No. 5,428, 128 (6/95).

The combined obviousness teaching of the Yagi and Ekwuribe patent references as discussed in the above rejection is hereby incorporated by reference in its entirety.

The combined teaching of Yagi and Ekwuribe further differ from the presently claimed (e.g. claim 94) which uses as therapeutic agent, Met-enkephalin modified by carboxyl addition of a lysine to effect Polyethylene glycol-alkyl attachment through a carbamate linkage via the epsilon aminolysine sidechain (e.g. Tyr-Gly-Gly-Phe-Met is Met-enkephalin) .

Initially, it is noted that Ekwuribe specifically suggests that the PEG of the oligomer be carbamate attached via an amino group to the polymer. E.e. see Ekwuribe at col. 14. In this regard, the Mensi-Fatthohi et al. reference teaches the carbamate attachment of PEG to opioid peptides thru a Lysine epsilon amino group in which the lysine is initially present or subsequently added to the opioid peptide. See Mensi-Fatthohi at col. 4 (lines 1-10; 20-40); examples, especially examples 9-10; and patent claims 1-29.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicants invention to further modify the enkephalin (e.g. Met-enkephalin) containing PEG-alkyl conjugates to attach (via a carbamate bond) by the use of an lysine epsilon amino group as taught by Mensi-Fatthohi in light of the Ekwuribe teaching of using amino groups for carbamate PEG attachment.

Double Patenting

7. Claims 46-47, 70-71, 73-81 and 98-100 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-60 of U.S. Patent No. 6,309,633 (10/01) in view of Yagi et al. US Pat. No. 5,061,691 (10/91) and further in view of the present specification (e.g. abstract; page 2 and Examples, especially on pages 44-48) as evidence of inherency.

The present claims are directed to:

A method of inducing analgesia in a subject in need thereof by administering a drug conjugate *which crosses the blood-brain barrier* in which the conjugate comprising:

a. an "opioid" (e.g. met enkephalin or leu enkephalin) conjugated to an

b. "oligomer", wherein the oligomer comprises "one or more lipophilic moieties" coupled to "one or more "hydrophilic moieties".

Preferred "opioids" are the pentapeptides met/leu enkephalins YGGFM and YGGFL, respectively (YGGFM elected);

Preferred "lipophilic moieties are fatty acids, cholesterol, and C1-C26 alkyl (alkyls elected);

Preferred "hydrophilic moieties" are sugars and PEG (PEG elected). See claims 46-49.

Additionally, the claims recite that the administered conjugate:

i. effects "CNS mediated" analgesia (E.g. see claims 46, 83 and claims 98-100);

ii. "traverses the blood brain barrier in an amount that is greater than a corresponding control" (new claim 98);

iii. "wherein a corresponding unconjugated control does not cross the blood-brain barrier in analgesically effective amounts" (new claim 99);

iv. "wherein the conjugate crosses the BBB in a controlled manner which permits accumulation of sufficient quantities of the therapeutic in the brain to induce analgesia" (new claim 100).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent claims teaches conjugates and pharmaceutical compositions and the administration thereof which comprise a drug oligomer complex in which the oligomer comprises a hydrophilic portion (E.g. PEG) and a hydrophobic portion (e.g. alkyl chain) in which the claimed drug can be selected from a group of preferred drugs which include opioids (e.g. see claim 34 which includes dynorphins, endorphins and enkaphilins) the selection of which would have been obvious since these represent most preferred (e.g. claimed) drug embodiments. The analgesic therapeutic use of the patented therapeutic compositions would have been obvious to one of ordinary skill in the art at the time of applicants invention upon *in vivo* delivery as taught by the Yagi et al. reference.

Additionally, the teaching of the '633 patent claims differ from the presently claimed invention (as amended) by failing to disclose or suggest that administration of an amphiplic drug-oligomer conjugate within the scope of the presently claimed invention achieves a delivery (of the conjugate) across the blood brain barrier of the subject in a "controlled manner which permits accumulation of sufficient quantities ... to induce analgesia".

However, in this respect it is noted that Yagi et al teach that

a. opiate (e.g. enkephalin) receptors are present in the brain (e.g. CNS) and are responsible for the analgesic effects of administered opioids (e.g. "CNS mediated analgesia" : see Yagi col. 1, especially lines 5-17);

b. unmodified (e.g. unconjugated) enkephalins produce a "weak and short-lived analgesia following i.c.v./i.v. administration to mice and rats (e.g unconjugated control does not cross the blood-brain barrier in analgesically effective amounts" and accordingly, the Yagi reference address efforts made (e.g. making of analogs of Met- and Leu-enkephalins) in order to promote *in vivo* delivery by overcoming art-recognized administration obstacles (e.g. enzymatic degradation*; ability to pass thru blood-brain* barrier; administration in oral dosage form etc.). See abstract; col. 1; and patent claims.

Additionally, the presently claimed method rendered obvious by the above-recited patents and references, must inherently produce the same *in vivo* effect (blood brain barrier delivery) because the same conjugate is applied (e.g. administered) in the same way in the same amount to the same subject. *In re Best*, 195 USPQ 430,433 (CCPA 1977). The specification provides evidence that the amphiphilic oligomer conjugates rendered obvious by the above references, are capable of (e.g. see present specification on page 2 and abstract) and indeed do traverse the blood brain barrier upon administration to subjects in the manner taught by the prior art references. See ***Ex parte Novitski***, 26 USPQ2d 1389 (B.P.A.I, 1993) (applicants own specification provides evidence of inherent effect produced upon drug administration); MPEP 2131.01(d) permits the citation of references or any other source of extrinsic evidence in order to show that a characteristic not disclosed in the reference is inherent.

8. Claims 46-49, 70-71, 73-76, 78-81, 83 , 85 and 98-100 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-60 of U.S. Patent No. 6,309,633 (10/01)and Yagi et al. US Pat. No. 5,061,691 (10/91). in view of Ekuwuribe US Pat. No. 5,681,811 alone and further in view of Mensi-Fattohi et al. US Pat. No. 5,428, 128 (6/95) and further in view of the present specification (e.g. abstract; page 2 and Examples, especially on pages 44-48) as evidence of inherency.

The combined '633 patent and Yagi patent obviousness teaching of the these reference recited above is hereby incorporated by reference in its entirety.

To the extent the presently claimed invention (e.g. claims 48-49, 83, 85) selects PEG (as hydrophilic moiety; preferably PEG2) and C1-C26 (as lipophilic moiety) the same is rendered obvious by Ekwuribe.

Ekwuribe teaches the preferential selection of PEG (especially PEG2-4) as the hydrophilic moiety and alkyls (e.g. CH3 and CH2mCH3 m is 1-125) as the lipophilic moiety in which the ADrug is attached through a carbamate linkage adjacent to the PEG region of the polymer with Athe point of attachment of the carbamate bond between the polymers preferably is the amine function . See col. 13-14, especially col. 13 (lines 5-20); col. 14 (conjugates 2 and 3); col 14 (lines 30-60); patent claims (especially claims 34 and conjugates 2 and 3 described therein and claims 35-42 drawn to therapeutic methods employing enkephalin conjugates). Ekwuribe further teaches the ability to vary the position and number of hydrophilic/lipophilic moieties to achieve optimization. E.g. see col. 14, lines 50-60.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize an oligomer (or polymer) comprising PEG (e.g. PEG2) as a hydrophilic moiety and a C1-26 alkyl in light of the Ekwuribe teaching of the preferred selection of PEG2-4 as a hydrophilic moiety and alkyls (e.g. m is 1-125 with methyl disclosed) with optimization of hydrophilic/lipophilic groups suggested by Ekwuribe in which such optimization is well within the skill of the art.

The combined teaching of patent '633, Yagi and Ekwuribe further differ from the presently claimed (e.g. claim 94) which uses as therapeutic agent, Met-enkephalin modified by carboxyl addition of a lysine to effect Polyethylene glycol-alkyl attachment through a carbamate linkage via the epsilon aminolysine sidechain (e.g. Tyr-Gly-Gly-Phe-Met is Met-enkephalin) .

Initially, it is noted that Ekwuribe specifically suggests that the PEG of the oligomer be carbamate attached via an amino group to the polymer. E.e. see Ekwuribe at col. 14. In this regard, the Mensi-Fatthohi et al. reference teaches the carbamate attachment of PEG to opioid peptides thru a Lysine epsilon amino group in which the lysine is initially present or subsequently added to the opioid peptide. See Mensi-Fatthohi at col. 4 (lines 1-10; 20-40); examples, especially examples 9-10; and patent claims 1-29.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicants invention to further modify the enkephalin (e.g. Met-enkephalin) containing PEG-alkyl conjugates to attach (via a carbamate bond) by the

use of an lysine epsilon amino group as taught by Mensi-Fatthohi in light of the Ekwuribe teaching of using amino groups for carbamate PEG attachment.

Additionally, the teaching of the '633 patent claims differ from the presently claimed invention (as amended) by failing to disclose or suggest that administration of an amphiplic drug-oligomer conjugate within the scope of the presently claimed invention achieves delivery (of the conjugate) across the blood brain barrier of the subject.

However, in this respect it is first noted that the Yagi et al. Reference teaches (e.g. see col. 1, particularly paragraph 4) that the molecular structure of synthetic enkephalins are designed to yield enkephalins which cross the blood-brain barrier. Accordingly, conjugate modification utilizing the Ekwuribe method would engender a *reasonable expectation* of achieving a conjugated enkephalin possessing not only the benefits of conjugation taught by Ekwuribe but also retention of the ability of the unconjugated peptides to cross the blood brain barrier since Ekwuribe teaches that the biological activity of its conjugated therapeutic compounds is retained following conjugation.

Additionally, the presently claimed method rendered obvious by the above-recited patents and references, must inherently produce the same *in vivo* effect (blood brain barrier delivery) because the same conjugate is applied (e.g. administered) in the same way in the same amount to the same subject. *In re Best*, 195 USPQ 430,433 (CCPA 1977). The specification provides evidence that the amphiphilic oligomer conjugates rendered obvious by the above references, are capable of (e.g. see present

specification on page 2 and abstract) and indeed do traverse the blood brain barrier upon administration to subjects in the manner taught by the prior art references. See ***Ex parte Novitski***, 26 USPQ2d 1389 (B.P.A.I, 1993) (applicant's own specification provides evidence of inherent effect produced upon drug administration); MPEP 2131.01(d) permits the citation of references or any other source of extrinsic evidence in order to show that a characteristic(s) not disclosed in the reference is inherent.

9. Claims 46-49, 70-71, 73-76, 78-81, 83, 85 and 98-100 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-44 of Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) and Yagi et al. US Pat. No. 5,061,691 (10/91); and further in view of the present specification (e.g. abstract; page 2 and Examples, especially on pages 44-48) as evidence of inherency.

The present claims are directed to:

A method of inducing analgesia in a subject in need thereof by administering a drug conjugate *which crosses the blood-brain barrier* in which the conjugate comprising:

a. an "opioid" (e.g. met enkephalin or leu enkephalin) conjugated to an

b. "oligomer", wherein the oligomer comprises "one or more lipophilic moieties" coupled to "one or more "hydrophilic moieties".

Preferred "opioids" are the pentapeptides met/leu enkephalins YGGFM and YGGFL, respectively (YGGFM elected);

Preferred "lipophilic moieties are fatty acids, cholesterol, and C1-C26 alkyl (alkyls elected);

Preferred "hydrophilic moieties" are sugars and PEG (PEG elected). See claims 46-49.

Additionally, the claims recite that the administered conjugate:

i. effects "CNS mediated" analgesia (E.g. see claims 46, 83 and claims 98-100);

ii. "traverses the blood brain barrier in an amount that is greater than a corresponding control" (new claim 98);

iii. "wherein a corresponding unconjugated control does not cross the blood-brain barrier in analgesically effective amounts" (new claim 99);

iv. "wherein the conjugate crosses the BBB in a controlled manner which permits accumulation of sufficient quantities of the therapeutic in the brain to induce analgesia" (new claim 100).

The Ekwuribe '811 patent claims teach the stabilization of therapeutic agents (E.g. protease resistance and enhanced penetration) for in vivo administration (e.g. oral or parenteral) by conjugating with a polymer which comprises lipophilic and hydrophilic moieties; with opioids, especially peptidic opioids such as endorphins and enkephalins being preferred therapeutic agents. See e.g. patent claims (especially claims 37-44). The Claimed therapeutic administration includes administration to humans via enteral (e.g. oral), parenteral, as well as other modes of physiological administration (E.g. see col. 12, especially lines 5-10; col. 13, especially lines 45-55; col. 24-col. 24) including ophthalmic, topical, bronchial, rectal, iv, subcutaneous, intrathecal etc (e.g. see col. 25-26). See also patent claims 35-44. The analgesic therapeutic use of the patented therapeutic compositions would have been obvious to one of ordinary skill in the art at the time of applicant's invention upon *in vivo* delivery as taught by the Yagi et al. reference which teaches the induction of analgesia by opioids (e.g endorphins/enkephalins) and the making of analogs of the peptide opioids Met- and

Leu-enkephalins in order to promote *in vivo* delivery by overcoming art-recognized administration obstacles (e.g. enzymatic degradation; ability to pass thru blood-brain barrier; administration in oral dosage form etc.). See abstract; col. 1; and patent claims.

To the extent the presently claimed invention (e.g. claims 48-49, 83, 85) selects PEG (as hydrophilic moiety; preferably PEG2) and C1-C26 (as lipophilic moiety) the same is rendered obvious by Ekwuribe.

Ekwuribe teaches the preferential selection of PEG (especially PEG2-4) as the hydrophilic moiety and alkyls (e.g. CH3 and CH2mCH3 m is 1-125) as the lipophilic moiety in which the Drug is attached through a carbamate linkage adjacent to the PEG region of the polymer with the point of attachment of the carbamate bond between the polymers preferably is the amine function. See col. 13-14, especially col. 13 (lines 5-20); col. 14 (conjugates 2 and 3); col 14 (lines 30-60); patent claims (especially claims 34 and conjugates 2 and 3 described therein and claims 35-42 drawn to therapeutic methods employing enkephalin conjugates). Ekwuribe further teaches the ability to vary the position and number of hydrophilic/lipophilic moieties to achieve optimization. E.g. see col. 14, lines 50-60.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicants invention to utilize an oligomer (or polymer) comprising PEG (e.g. PEG2) as a hydrophilic moiety and a C1-26 alkyl in light of the Ekwuribe teaching of the preferred selection of PEG2-4 as a hydrophilic moiety and alkyls (e.g. m is 1-125 with methyl disclosed) with optimization of hydrophilic/lipophilic groups suggested by Ekwuribe in which such optimization is well within the skill of the art.

Additionally, the teaching of the '811 patent claims differ from the presently claimed invention (as amended) by failing to disclose or suggest that administration of an amphiplic drug-oligomer conjugate within the scope of the presently claimed invention achieves delivery (of the conjugate) across the blood brain barrier of the subject.

However, in this respect it is noted that Yagi et al teach that

a. opiate (e.g. enkephalin) receptors are present in the brain (e.g. CNS) and are responsible for the analgesic effects of administered opioids (e.g. "CNS mediated analgesia" : see Yagi col. 1, especially lines 5-17);

b. unmodified (e.g. unconjugated) enkephalins produce a "weak and short-lived analgesia following i.c.v./i.v. administration to mice and rats (e.g unconjugated control does not cross the blood-brain barrier in analgesically effective amounts" and accordingly, the Yagi reference address efforts made (e.g. making of analogs of Met- and Leu-enkephalins) in order to promote *in vivo* delivery by overcoming art-recognized administration obstacles (e.g. enzymatic degradation*; ability to pass thru blood-brain* barrier; administration in oral dosage form etc.). See abstract; col. 1; and patent claims.

Additionally, the presently claimed method rendered obvious by the above-recited patents and references, must inherently produce the same *in vivo* effect (blood brain barrier delivery in a controlled manner ... of sufficient quantitities ... to induce analgesia) because the same conjugate is applied (e.g. administered) in the same way in the same amount to the same subject. *In re Best*, 195 USPQ 430,433 (CCPA 1977). The specification provides evidence that the amphiphilic oligomer conjugates rendered

obvious by the above references, are capable of (e.g. see present specification on page 2 and abstract) and indeed do traverse the blood brain barrier upon administration to subjects in the manner taught by the prior art references. See ***Ex parte Novitski***, 26 USPQ2d 1389 (B.P.A.I, 1993) (applicants own specification provides evidence of inherent effect produced upon drug administration); MPEP 2131.01(d) permits the citation of references or any other source of extrinsic evidence in order to show that a characteristic not disclosed in the reference is inherent.

10. Claims 46-49, 70-71, 73-76, 78-81, 83, 85 and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) and Yagi et al. US Pat. No. 5,061,691 (10/91) as applied to claims 46-49, 70-71, 73-76, 78-81, 83, 85 and 98-100 above, and further in view of Mensi-Fattohi et al. US Pat. No. 5,428, 128 (6/95); and still further in view of the present specification (e.g. abstract; page 2 and Examples, especially on pages 44-48) as evidence of inherency.

The combined obviousness teaching of the Yagi and Ekwuribe patent claims as discussed in the above rejection is hereby incorporated by reference in its entirety.

The combined teaching of Yagi and Ekwuribe further differ from the presently claimed (e.g. claim 94) which uses as therapeutic agent, Met-enkephalin modified by carboxyl addition of a lysine to effect Polyethylene glycol-alkyl attachment through a carbamate linkage via the epsilon aminolysine sidechain (e.g. Tyr-Gly-Gly-Phe-Met is Met-enkephalin) .

Initially, it is noted that Ekwuribe specifically suggests that the PEG of the oligomer be carbamate attached via an amino group to the polymer. E.e. see Ekwuribe at col. 14. In this regard, the Mensi-Fatthohi et al. reference teaches the carbamate attachment of PEG to opioid peptides thru a Lysine epsilon amino group in which the lysine is initially present or subsequently added to the opioid peptide. See Mensi-Fatthohi at col. 4 (lines 1-10; 20-40); examples, especially examples 9-10; and patent claims 1-29.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicants invention to further modify the enkephalin (e.g. Met-enkephalin) containing PEG-alkyl conjugates to attach (via a carbamate bond) by the use of an lysine epsilon amino group as taught by Mensi-Fatthohi in light of the Ekwuribe teaching of using amino groups for carbamate PEG attachment.

Additionally, the teaching of the >811 patent claims differ from the presently claimed invention (as amended) by failing to disclose or suggest that administration of an amphiphilic drug-oligomer conjugate within the scope of the presently claimed invention achieves Adelivery (of the conjugate) across the blood brain barrier of the subject≅.

However, in this respect it is first noted that the Yagi et al. Reference teaches (e.g. see col. 1, particularly paragraph 4) that the molecular structure of synthetic enkephalins are designed to yield enkephalins which cross the blood-brain barrier. Accordingly, conjugate modification utilizing the Ekwuribe method would engender a *reasonable expectation* of achieving a conjugated enkephalin possessing not only the

benefits of conjugation taught by Ekwuribe but also retention of the ability of the unconjugated peptides to cross the blood brain barrier since Ekwuribe teaches that the biological activity of its conjugated therapeutic compounds is retained following conjugation.

Additionally, the presently claimed method rendered obvious by the above-recited patents and references, must inherently produce the same *in vivo* effect (blood brain barrier delivery) because the same conjugate is applied (e.g. administered) in the same way in the same amount to the same subject. *In re Best*, 195 USPQ 430,433 (CCPA 1977). The specification provides evidence that the amphiphilic oligomer conjugates rendered obvious by the above references, are capable of (e.g. see present specification on page 2 and abstract) and indeed do traverse the blood brain barrier upon administration to subjects in the manner taught by the prior art references. See ***Ex parte Novitski***, 26 USPQ2d 1389 (B.P.A.I, 1993) (applicant=s own specification provides evidence of inherent effect produced upon drug administration); MPEP 2131.01(d) permits the citation of references or any other source of extrinsic evidence in order to show that a characteristic not disclosed in the reference is inherent.

New Objection (s) and/or Rejection (s)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-49, 70-71, 73-76, 78-81, 83, 85, and 98-100 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (NEW MATTER REJECTION)

a. In claims 46 and 83 (and claims dependent thereon), the phrases "analgesia *mediated in the central nervous system*" (claims 46 and 83) and "central nervous system-mediated analgesia" (new claims 98-100) constitute new matter since there is no specification support (nor has applicant indicated where support exists) for "mediated in the central nervous system" or "central nervous system-mediated" as presently claimed.

b. In new claims 98-100 the phrases comprising the "wherein" clauses which are presented within the last three lines of these claims (e.g. "wherein the conjugate traverses the blood brain barrier in an amount that is greater than a corresponding unconjugated control" constitutes new matter since there is a lack of specific support for such "wherein" language nor is there commensurate support for the scope of the generic claim (e.g. for any amphiphilic opioid drug-oligomer conjugate). The specification showing of a small number of specific peptides (E.g. specification pages 46-48, especially table on page 47) regarding "mean analgesia" for @5min (and 30 min) as compared to morphine and enkephalin fails to provide commensurate support for the claimed generic scope as well as the language recited in the "wherein" clauses

(e.g. referring to "amount that is greater" in claim 98; the inability to cross in analgesic amounts in claim 99; and "controlled manner", "permits accumulation of sufficient quantitities" in claim 100) which is not specifically supported or derivable from the tabulated data provided.

Claims 46-49, 70-71, 73-76, 78-81, 83, 85, and 98-100 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (lack of written description).

The present claims are directed to:

A method of inducing analgesia in a subject in need thereof by administering a drug conjugate which crosses the blood-brain barrier in which the conjugate comprising:

a. an "opioid" (e.g. met enkephalin or leu enkephalin) conjugated to an

b. "oligomer",

wherein the oligomer comprises "one or more lipophilic moieties" coupled to "one or more "hydrophilic moieties".

The terms "hydrophilic/ hydrophobic moiety" are broadly defined in the specification (e.g. ability to dissolve in water/lipid and/or increase hydrophilicity/hydrophobicity of the chemically attached entity). Accordingly, the claimed conjugates encompass opioid conjugated to purely functional groups (E.g. one or more hydrophilic/ hydrophobic moieties which are structureless) which are unlimited as to point of attachment to the "opioid" compound which must possess the ability to cross the blood-brain barrier; and with regard to the new claims further meet the

additional "wherein limitations" presented in the last three lines of new claims 98-100. Regarding the "wherein limitations", the discussion above presented in the new matter rejection of these claims is herein incorporated by reference in its entirety.

In support thereof, the specification describes a small number of specific conjugate species which comprise:

a. met/leu enkephalin pentapeptides (or C-terminal lys derivatives thereof) as opioids which are specifically attached to specific oligomers (e.g. fatty acid; alkyl; cholesteryl, adamantine, sugar as lipophilic groups; and PEG and derivatives as hydrophobic groups) at specific positions (e.g. lys side chain); and a smaller number of species (E.g. four peptide enkephalin peg derivatives) which pass the blood-brain barrier (e.g. see table on page 47 of specification).

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)]. See also "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001). It is additionally noted that written description is legally distinct from enablement: "Although the two concepts of are entwined,

they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures the that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co.* In this regard, applicant is further referred to *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997); "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001).

Accordingly, the small number of disclosed and the even smaller number of tested specific enkephalin drug conjugates demonstrated to possess the ability to cross the blood-brain barrier fails to provide adequate written description for the scope of the presently claimed generic of opioid-oligomer conjugates.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claims 46-48, 70-71, 73-76, 78-81 and 98-100 are rejected under 35 U.S.C. 102(b) as being anticipated by Shashoua US Pat. No. 4,933,324 (6/90) and STN: Biosequence Searching For the USPTO (May 1996) pages 30-31 cited to demonstrate "inherency".

The present claims are directed to:

A method of inducing analgesia in a subject in need thereof by administering a drug conjugate, which crosses the blood-brain barrier in which the conjugate comprising:

a. an "opioid" (e.g. met enkephalin or leu enkephalin) conjugated to an

b. "oligomer",

wherein the oligomer comprises "one or more lipophilic moieties" coupled to "one or more "hydrophilic moieties".

Shasoua disclose fatty acid neuoroactive drug conjugates which cross the blood-brain barrier and pharmaceutical compositions thereof for broad (e.g. oral/parenteral, rectal, topical peritoneal, iv : eg. See col. 12, abstract, patent claims) administration to patients (e.g. animals or humans) in need thereof .

The Shasoua reference further encompasses met enkephalin a derivative thereof which is attached to a fatty acid compound for pharmaceutical therapy (e.g. see patent claims and particularly patent claims 1, 15, 17-24, 38, 40-48) which includes fatty acid derived YGGFMK compound administered to a mammal (E.g mouse) for its improved (as compared to corresponding "unconjugated controls") analgesic properties e.g. by its ability to traverse the blood-brain barrier (e.g. see e.g. col. 11).

The reference compound is within the scope of the presently claimed invention since the reference conjugate comprises:

A. met-enkephalin (e.g. Tyr-Gly-Gly-Phe-Met: or YGGFMK) covalent attached to an oligomer comprising

b. one hydrophilic moiety (e.g. lysine or K) coupled to

c. one lipophilic moiety (e.g. fatty acid).

See : STN: Biosequence Searching For the USPTO (May 1996) pages 30-31 at page 31 to teach that lysine is inherently a "hydrophilic" amino acid (e.g. contains a hydrophilic moiety).

The ability of the reference met-enkephalin derivative to be efficacious at tenfold lower doses than free met-enkephalin (e.g. see col. 11, lines 7-30) indicates that the reference derivative will cross the blood brain barrier in low amounts unlike free met-enkephalin and in amounts controlled and accumulated to insure therapy e.g. directly or inherently anticipating (e.g. conjugate administered to same host in amounts w/n claim scope) the "wherein" clauses presented in new claims 99-100.

11. Claims 46-49, 70-71, 73-76, 78-81, 85 and 98-100 are rejected under 35 U.S.C. 102(a,e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ekwuribe et al. US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) in view of Yagi et al. US Pat. No. 5,061,691 (10/91) and Shashou US Pat. No. 4,933,324 (6/90) as evidence of enablement, term meaning, and inherency regarding the primary Ekwuribe reference. See MPEP 2131.01 (multiple reference 102) and MPEP 2131.02 (genus-species anticipation).

The present claims are directed to:

A method of inducing analgesia in a subject in need thereof by administering a drug conjugate *which crosses the blood-brain barrier* in which the conjugate comprising:

a. an "opioid" (e.g. met enkephalin or leu enkephalin) conjugated to an

b. "oligomer", wherein the oligomer comprises "one or more lipophilic moieties" coupled to "one or more "hydrophilic moieties".

Preferred "opioids" are the pentapeptides met/leu enkephalins YGGFM and YGGFL, respectively (YGGFM elected);

Preferred "lipophilic moieties are fatty acids, cholesterol, and C1-C26 alkyl (alkyls elected);

Preferred "hydrophilic moieties" are sugars and PEG (PEG elected). See claims 46-49.

Additionally, the claims recite that the administered conjugate:

i. effects "CNS mediated" analgesia (E.g. see claims 46, 83 and claims 98-100);

ii. "traverses the blood brain barrier in an amount that is greater than a corresponding control" (new claim 98);

iii. "wherein a corresponding unconjugated control does not cross the blood-brain barrier in analgesically effective amounts" (new claim 99);

iv. "wherein the conjugate crosses the BBB in a controlled manner which permits accumulation of sufficient quantities of the therapeutic in the brain to induce analgesia" (new claim 100). Claim 85 is drawn to the elected alkyl-Peg "oligomer" subgeneric

Ekwuribe teaches the stabilization of therapeutic agents (E.g. protease resistance and enhanced penetration) for in vivo administration (e.g. oral or parenteral; to humans or animals: compare col. 2/24/ and col. 25, especially lines 1-15 and present claims 74-76) by conjugating with a polymer which comprises lipophilic and hydrophilic moieties. E.g. see abstract; col 1-4 (e.g. stabilization). Opioids, especially peptidic opioids such as endorphins and enkephalins are preferred therapeutic agents. See Abstract; col. 8 (lines 40-50); patent claims (especially claims 37-44).

More particularly, Ekwuribe disclose and claim (e.g. claims 35-39) pharmaceutical compositions for use in:

a. "therapeutic methods" and

b. "prolonging the activity of a therapeutically active agent"

in which the selection of the "therapeutic" as one or more of "an endorphin", "enkephalin" or a "non-naturally occurring opioid" (all within the scope of the present claims) from among a CLAIM Markush (e.g. claim 37) of only 41 possibilities is envisaged (e.g. anticipated) or alternatively prima facie obvious to one of ordinary skill in the art. See e.g. MPEP 2131.02 and case law cited therein, where a Markush listing that clearly names the species is anticipatory, or in the alternative prima facie obvious. Similarly, the '811 disclosure (e.g.; col. 14 conjugates 2 and 3; patent claim 34 col. 36, especially lines 20-30) preferred teaching of alkyl PEG oligomer as the lipophilic/hydrophilic moiety as presently claimed (e.g. claim 85) would be anticipated or

prima facie obvious in light of the clear reference teaching of this subgeneric (e.g. in the patent disclosure) and/or the selection of this subgeneric from a limited CLAIMED Markush.

Although Ekwuribe discloses and claims "therapeutic" pharmaceutical compositions comprising opioids, enkephalins and endorphins including administration (e.g. oral/parenteral to human or animals) and amounts within the scope of the presently claimed invention. the patent reference fails to explicitly disclose :

a. the present "analgesic" use of enkephalins and that

b. enkephalins encompass the pentapeptide met-enkephalin of sequence Tyr-Gly-Gly-Phe-Met.

The Ekwuribe (disclosed and claimed) administration of a "therapeutic" method comprising the administration of opioids (e.g. met- enkephalin)is enabled: since it was well known in the art at the time of the filing of the Ekwuribe patent that enkephalin induced analgesia through interaction with opiate brain receptors and thus:

a. enkephalin was conventionally known to be useful in "pain" therapy and

b. additionally encompassed met-enkephalin (and Leu-enkephalin) of sequence YGGFM(L) where M is methionine and L is leucine.

See Yagi et al. col. 1; Shasou at col. 11.

Accordingly, the Ekwuribe patent disclosure and claiming of an an enabled "analgesic" therapeutic method of administering opioids, enkephalins (e.g. Met-enkephalin) in amounts, means and to hosts within the scope of the presently claimed invention would inherently result in the conjugated reference peptide crossing the blood brain barrier in amounts greater than the unconjugated peptide and in amount and in a controlled manner necessary to accumulate to insure therapy . See MPEP 2112 and 2112.02 wherein prior art teaching of method steps

anticipates (e.g. as discussed above) and an old composition does not become patentable upon "the discovery of a previously unappreciated property of a prior art composition" (e.g. in this case ability to penetrate blood brain barrier).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
September 21, 2004